UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF OHIO
EASTERN DIVISION

IN RE NATIONAL PRESCRIPTION OPIATE LITIGATION **This document relates to**: *Track Three Cases*	**MDL No. 2804** **Case No. 17-md-2804** **Judge Dan Aaron Polster**

DECLARATION OF STEVEN N. HERMAN IN SUPPORT OF THE PHARMACY DEFENDANTS' MOTION TO EXCLUDE CERTAIN OPINIONS AND TESTIMONY OF DR. KATHERINE KEYES

EXHIBIT 2

CONFIDENTIAL

Katherine Keyes expert witness report

I. Background and Qualifications

A. Summary

I am an Associate Professor of Epidemiology at Columbia University, specializing in substance use and substance use disorders epidemiology.

B. Education

I received a Masters degree in Public Health from Columbia University in 2004, and a PhD in Epidemiology from Columbia University in 2010.

C. Field of specialty and employment history

My field of specialty is substance use and substance use disorders, as well as related comorbidity, focusing on psychiatric disorders, and consequences of substance use including intentional and unintentional injury. After receiving my PhD in Epidemiology in 2010, I completed a post-doctoral fellowship in Epidemiology at Columbia University from 2010 through 2012, and then was recruited by Columbia University to join the faculty in 2012 as a tenure-track Assistant Professor. I was promoted to Associate Professor in 2016. I also hold academic appointments at various other universities. I am a Research Assistant Professor at the University of Michigan, and an Adjunct Associate Professor at the Society for Health and Research at Universidad Mayor in Santiago, Chile.

D. Research areas and publications

I have published 225 peer-reviewed articles and book chapters, more than 60 of which are first-authored. Much of this research has been published in the leading, highest impact epidemiology, psychiatry, and substance use journals, including in *Pediatrics, JAMA Psychiatry, Lancet Psychiatry, Nature Communications, British Medical Journal, British Journal of Psychiatry, American Journal of Psychiatry, American Journal of Epidemiology,* and *International Journal of Epidemiology*, among others. My articles have been cited in numerous disciplines, including psychiatry, epidemiology, public health, and pediatrics. My *h*-index ranges from 43 (Web of Science) to 60 (Google Scholar)[1]. Currently, 50 of my articles have been cited more than 100 times; 15 of my articles have been cited more than 200 times; and 4 have been cited more than 500 times. Since obtaining my doctoral degree, I have led numerous and sustained extramurally funded grants as Principal Investigator, and have successfully competed for grant funding from the National Institutes of Health to conduct my research. I have received numerous grants from Columbia University for my work, including the Calderone Prize for junior faculty, and the Tow scholarship (awarded to high-achieving mid-career scientists). I serve as a co-Investigator on numerous federally-funded grants both at Columbia and at other institutions (including University of Michigan and New York University).

I have published two textbooks on epidemiological methods, and I am well-qualified to assess the literature on opioid-related harm. The first is *Epidemiology Matters: A New Introduction to Methodological Foundations*, published by Oxford University Press in 2014, which is currently being used to teach graduate students about epidemiological methods in more than 20 universities. The second is *Population Health Science*, also published

[1] An h-index is a measure of productivity and research impact. It is the median level of correlation between number of peer-reviewed papers and the number of times each paper has been cited for a given scholar. As such, an h-index of 60 indicates that I have published a median of 60 papers that have been cited at least 60 times. Benchmarks for h-indices vary; at Columbia University department of epidemiology, the standards for promotion are an h-index of at least 15 for promotion to Associate Professor, and at least 25 for promotion to professor. My h-index is more than twice that needed for a full professor rank in my department at Columbia University, indicative of high productivity and impact.

applicable to the question at hand (e.g. risk of opioid use disorders among those prescribed opioids), I considered meta-analysis and systematic reviews to be high levels of evidence, and cite them as well as discuss their findings when they are available. Systematic reviews and meta-analysis are considered high levels of evidence because they quantitatively and qualitatively assess the overall body of the literature and provide quality assessments that weight evidence based on reproducible standards. I consider studies that had prospective follow-up of patients or participants, a well-described strategy for statistical control of confounders, and well-designed comparison groups to be the next level of evidence. Prospective follow-up is an important study design because it reduces biases in epidemiological studies from retrospective reporting of symptoms or events. Further, statistical controls are necessary to overcome the potential for bias from confounding. Prospective studies often involve comparison groups (e.g. prescription opioid users and a comparison group of non-prescription opioid users). Study designs with comparison groups provide evidence regarding opioid-related harm that is over and above harm in patient and general population samples across varying levels of opioid exposure. Studies of patient populations without comparison groups, however, are additionally informative particularly for research questions germane to the prevalence of opioid use disorders and related harm among patients prescribed opioids, especially high doses in long duration, as well as questions related to the proportion of drug users who previously used prescription opioids. Well-designed studies of single populations without explicit comparison groups are thus also considered as relevant evidence for characterization of prescription opioid-related harms.

With regard to studies that assess trends over time, I considered three data sources to be the highest levels of evidence. First, I relied on death records that are collected and harmonized by the national vital statistics surveillance system. While death records can have misclassification of causes of death, they are considered by experts to be a reliable indicator of national and local burden of specific causes of death, especially when examining trends over time. Second, I relied on data sources with national reputation for transparency in reliability and validity that assess hospitalization and other clinical records, such as large electronic health databases. Again, while hospital records can include misclassification, data sources gathered from reputable organizations such as the Agency for Healthcare Research and Quality include reliability and validity assessments that allow the researcher using them to be able to draw conclusions based on the best available evidence. Third, I relied on survey data that is routinely collected in the general population of households in the United States over time. Surveys are essential parts of surveillance, given that many cases of substance use disorder do not come to clinical attention, and thus relying on clinically ascertained records can give a biased assessment of trends and burden in the population. Survey data source methodology is to do clustered sampling so that samples are representative of the entire US, and respondents are interviewed with validated instruments that are designed to elicit diagnoses and information with maximum accuracy in the survey context. Generally, I do not include surveys that are not representative of the population or based on samples, as they are not strong evidence for an assessment of the total burden and trends over time.

IV. Detailed Statement of Opinions

B.1. Distribution, sales, and marketing of opioids increased in the 1990s.

There is voluminous evidence regarding the distribution, sales, and marketing of opioids beginning in the 1990s. This evidence is the subject of other witnesses' reports, and I will not repeat all of that evidence here. Instead, I will summarize some points for context. Opioid pain relievers became an increasingly widely-used option starting in the early 1990s, particularly for chronic non-cancer pain, a use that had rarely been seen previously. Estimates from the Automation of Reports and Consolidated Orders System (ARCOS), which tracks prescription distribution and sales, indicate that prescription opioids were dispensed at a range of 96 mg per person in 1997, and increased to 700 mg per person by 2007 (>600% increase).[11,12] . In 1995, the year OxyContin entered the market, the number of prescriptions filled in the US increased by 8 million, and continued to increase over the next two decades before peaking in the fourth quarter of 2010 at 62 million prescriptions dispensed.[13,14] From 1997 to 2002, prescriptions for OxyContin for non-cancer pain increased from approximately 670 000 in 1997 to about 6.2 million in 2002 (prescriptions for cancer pain also increased, about four-fold, across the same period).[15] The supply of opioids was driven by a multitude of

factors, including direct marketing to physicians using data that underestimated opioid use diosrder risks in patients, which I will detail in Section B.2. Evidence shows that pharmaceutical marketing of prescription drugs increases prescribers' likelihood of prescribing the marketed drug in the future,[16,17] including prescription opioids, and resulted in increased sales of the marketed drugs.

Based on this evidence, the rapid increase in total opioid prescribing levels after the introduction of OxyContin in 1996 was driven by marketing and sales of opioids to physicans due to downplaying risks of harms associated with prescribing, including opioid use disorder and overdose.

Evidence published in 2019 indicates that the supply of opioids through prescriptions shows some evidence of decline in recent years, and yet the supply remains high in volume, and significantly higher than it was in the mid 1990s. Data from outpatient prescribing records from IQVIA Xponent database, covering 59,400 pharmacies (representing 92% of retail prescriptions dispensed in the US) examined trends from 2006 through 2017 in milligrams of prescribed opioids, duration per prescription, high doseage prescription fills (>= 90 MME/day), prescriptions filled for 3 days or fewer and 30 days or longer, and extended-released/long-acting formulation prescriptions. While there are overall declines in opioid prescribing, and high dose prescribing, the supply of opioids remains high in volume and prescription length continues to increase. Opioid prescriptions per person in the total US increased annually at an average rate of 6.9% per year until 2010, and decreased at an average rate of 3.8% per year from 2010 through 2015. In 2017, there remained a high level of opioid prescribing in the US, with 191,218,266 prescriptions dispensed, leading authors to conclude that still in 2017 "pharmacies filled enough opioid prescriptions to theoretically provide every US resident with 5 mg of hydrocodone bitartrate every 4 hours around the clock for 3 weeks." Hydrocodone bitartrate has several formulations, including hydrocodone bitartrate with acetaminophen commonly known as Vicodin. Focusing on Ohio in particular, trends mirror the national averages, although there is evidence of a stronger decline in Ohio compared to the national average in recent years. In particular, MME per person increased in Ohio by an average of 6.1% per year from 2006 through 2010; decreased on average by 6.7% per year from 2010 through 2015, and decreased 12.7% per year from 2015 through 2017. Duration per prescription has increased in Ohio throughout the period of 2006 through 2017 (12.4 days in 2006 to 19.3 days in 2017), at an average rate of 4.1 % increase per year.

B.2. Risks of opioid use disorder following medical use of prescription opioids follow a "dose-response" pattern

Early studies cited in marketing materials to physicians underestimated the addiction potential of prescription opioids, and included claims that risks of opioid use disorders are rare among those prescribed opioids. Much of the material provided to physicians on the risks of opioid use disorders after medical prescription of opioids, however, was based on studies that were inadequate epidemiologically, such as Porter and Jick (1980),[18] which did not examine risk of use disorder or dependence based on dose or length of use of opioids, and did not use validated or objective assessments of opioid use disorder. Further, the doses, conditions, and range of medications actually provided to patients often differed from what was cited in these studies. Since early reports, the accumulated evidence regarding the risks of opioid use disorder suggest that the prevalence of opioid use disorder following medical use of prescription opioids is higher than cited in pharmaceutical materials, that the risk escalates with increasing dose, and that both new and recurrent opioid use disorders have higher risk than baseline following a medical prescription.

For this report I reviewed six systematic reviews and/or meta-analyses that assessed opioid use disorder among medical users of opioids.

Vowles et al. (2015)[19] provides the most transparent and high-quality review of the evidence of opioid use disorder among patients prescribed opioids for chronic pain. Vowles et al. (2015), unlike other reviews, calculated estimates of prevalence of three outcomes: (1) misuse, described by Vowles et al. as using opioids contrary to directed or prescribed; (2) abuse, described as intentional use of opioids for euphoric effects; (3)

(correlations ranged from 0.76 to 0.87). Taken together, these data indicate strong and statistically significant correlations between opioid supply and prescribing practices, and opioid-related harm in the US population.

Pharmaceutical company marketing to physicians, often based on sources that underestimated the risk of opioid use disorder, harm, and diversion, as discussed in Section B.2., contributed to the increase in the supply of opioids.[15] These marketing practices led to consequences for opioid-related harm. Pharmacuetical company marketing to physicans is extensive in the United States.[17] Empirical evidence has demonstrated that industry payments to physicians as part of the marketing of prescription opioids were associated with increased opioid prescriptions,[69] and that 1 in 12 physicians in the US, and 1 in 5 family physicians, received opioid-related marketing.[17,69–71] Hadland et al. (2019)[72] used data form the Centers for Medicare & Medicaid Service Open Payments database to assess the monetary value in payments to physicians for opioid products in all US counties over time, as well as data on dispensing of opioids in available counties in the US, and examined the spatial and temporal correlations with prescription opioid deaths as designed in the vital statistics records. Authors used a rigorous statistical model that included controls for a range of county-level factors such as economic environment (e.g. unemployment, income, income inequality) as well as demographics. Results demonstrated that even with statistical controls in place, each one standard deviation increase in payments to physicians was associated with statistically significant increases in prescription opioid overdose; including when marketing was assessed by marketing value in dollars per capita (each standard deviation increase associated with 1.09 times the rate of death), number of payments to physicians per capita (each standard deviation increase associated with 1.18 times the rate of death), and number of physicians receiving marketing per capita (each standard deviation increase associated with 1.12 times the rate of death). Further, these authors conducted mediation analysis to quantitatively demonstrate that the association between marketing to physicians and prescription opioid overdose was mediated by (that is, explained by) the increase in opioid prescribing and increased distribution. However, it is important to note that payments to physicians are only one type of promotional activity, and accounted for only a proportion of the overall promotion strategy for opioid pharmacueticals. These results are highly rigorous and clearly demonstrate harm to the population from opioid marketing and distribution.

Finally, a working paper authored by Powell et al. (2015)[73] examined the introduction of the Medicare Prescription Drug Benefit (Part D) program in 2006 as a potential driver of the opioid supply among those aged 65+. This paper is particularly relevant given the quasi-experimental design of using an exposure with exogenous variation, and a new law passed heterogeneously across states, to assess changes in the opioid supply. "Exogenous variation" is a term that is commonly used in epidemiological and economics literature to mean that there is no possibility that confounding factors such as increased prevalence of pain, or increased risk factors for addiction, could explain changes in the exposure. Thus, changes in the Medicare system cannot be caused by users of that system, and as such, associations between changes in the Medicare system and changes in opioid supply are more likely to be causal. Using data from 1999 through 2016, authors documented that the Medicare expansion affected the opioid supply, with states that had a relatively larger proportion of individuals gaining access to prescription drug coverage exhibiting an increase in opioid supply based on ARCOS data. Further, authors examined correlations with drug overdose deaths, and specifically those with codes that indicate prescription opioid poisoning, as well as substance abuse treatment admissions, an indicator of the occurrence of opioid use disorders. For both prescription deaths and treatment admissions, there was evidence that the increase in the opioid supply was associated with increases in deaths and treatment admissions; results were robust to a range of sensitivity analyses, alternative modeling of the statistical associations, and a range of quasi-experimental statistical models. As such, these data reinforce the conclusion that the opioid supply directly affects opioid-related harm, and provide a strong design and test of the hypothesis using the quasi-experimental instrument of changes in Medicare prescription coverage.

References

1. Negussie Y, Geller. Getting to Zero Alcohol-Impaired Driving Fatalities: A Comprehensive Approach to a Persistent Problem. Negussie Y, Geller A, Teutsch SM, eds. January 2018. doi:10.17226/24951
2. Hughes A, Williams M, Lipari RN, Bose J, Copello EAP, Kroutil LA. Prescription Drug Use and Misuse in the United States: Results from the 2015 National Survey on Drug Use and Health. *NSDUH Data Rev.* 2016.
3. Slavova S, O'Brien DB, Creppage K, et al. Drug Overdose Deaths: Let's Get Specific. *Public Health Rep.* 2015;130(4):339-342. doi:10.1177/003335491513000411
4. Ruhm CJ. Deaths of Despair or Drug Problems? *NBER Work Pap Ser.* 2018;24188.
5. Keyes KM, Galea S. *Epidemiology Matters: A New Introduction to Methodological Foundations.* Oxford University Press; 2014.
6. Callaham ML, Baxt WG, Waeckerle JF, Wears RL. Reliability of editors' subjective quality ratings of peer reviews of manuscripts. *JAMA.* 1998;280(3):229-231.
7. DeVito NJ, Goldacre B. Catalogue of bias: publication bias. *BMJ Evidence-Based Med.* December 2018. doi:10.1136/bmjebm-2018-111107
8. Goldacre B, Drysdale H, Marston C, et al. COMPare: Qualitative analysis of researchers' responses to critical correspondence on a cohort of 58 misreported trials. *Trials.* 2019;20(1):124. doi:10.1186/s13063-019-3172-3
9. Fontanarosa P, Bauchner H. Conflict of Interest and Medical Journals. *JAMA.* 2017;317(17):1768-1771. doi:10.1001/jama.2017.4563
10. Ahn R, Woodbridge A, Abraham A, et al. Financial ties of principal investigators and randomized controlled trial outcomes: cross sectional study. *BMJ.* 2017;356:i6770. doi:10.1136/bmj.i6770
11. Paulozzi LJ, Baldwin GT, Franklin GM, et al. CDC Grand Rounds: Prescription Drug Overdoses—a U.S. Epidemic. *Morb Mortal Wkly Rep.* 2012;61(01):10-13.
12. US Department of Justice; Drug Enforcement Administration. Automation of Reports and Consolidated Orders System (ARCOS). https://www.deadiversion.usdoj.gov/arcos/index.html.
13. Dart RC, Surratt HL, Cicero TJ, et al. Trends in Opioid Analgesic Abuse and Mortality in the United States. *N Engl J Med.* 2015;372(3):241-248. doi:10.1056/NEJMsa1406143
14. Volkow ND. *America's Addiction to Opioids: Heroin and Prescription Drug Abuse.*; 2014.
15. Van Zee A. The Promotion and Marketing of OxyContin: Commercial Triumph, Public Health Tragedy. *Am J Public Health.* 2009;99(2):221-227. doi:10.2105/AJPH.2007.131714
16. Fickweiler F, Fickweiler W, Urbach E. Interactions between physicians and the pharmaceutical industry generally and sales representatives specifically and their association with physicians' attitudes and prescribing habits: a systematic review. *BMJ Open.* 2017;7(9):e016408. doi:10.1136/bmjopen-2017-016408
17. DeJong C, Aguilar T, Tseng C-W, Lin GA, Boscardin WJ, Dudley RA. Pharmaceutical Industry–Sponsored Meals and Physician Prescribing Patterns for Medicare Beneficiaries. *JAMA Intern Med.* 2016;176(8):1114-1122. doi:10.1001/jamainternmed.2016.2765
18. Porter J, Jick H. Addiction rare in patients treated with narcotics. *N Engl J Med.* 1980;302(2):123.
19. Vowles KE, McEntee ML, Julnes PS, Frohe T, Ney JP, van der Goes DN. Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. *Pain.* 2015;156(4).
20. Meltzer EC, Rybin D, Saitz R, et al. Identifying prescription opioid use disorder in primary care: diagnostic characteristics of the Current Opioid Misuse Measure (COMM). *Pain.* 2011;152(2):397-402. doi:10.1016/j.pain.2010.11.006
21. Jamison RN, Butler SF, Budman SH, Edwards RR, Wasan AD. Gender Differences in Risk Factors for Aberrant Prescription Opioid Use. *J Pain.* 2010;11(4):312-320. doi:https://doi.org/10.1016/j.jpain.2009.07.016
22. Edlund M, Sullivan M, Steffick D, Harris K, Wells K. Do users of regularly prescribed opioids have higher rates of substance use problems than nonusers? *Pain Med.* 2007;8(8):647-656.

67. Paulozzi LJ, Mack KA, Jones CM. Vital Signs: Risk for Overdose from Methadone Used for Pain Relief—United States, 1999-2010. *Morb Mortal Wkly Report2*. 2012;61.
68. Wisniewski AM, Purdy CH, Blondell RD. The epidemiologic association between opioid prescribing, non-medical use, and emergency department visits. *J Addict Dis*. 2008;27(1):1-11. doi:10.1300/J069v27n01_01
69. Hadland SE, Cerda M, Li Y, Krieger MS, Marshall BDL. Association of Pharmaceutical Industry Marketing of Opioid Products to Physicians With Subsequent Opioid Prescribing. *JAMA Intern Med*. 2018;178(6):861-863. doi:10.1001/jamainternmed.2018.1999
70. Yeh JS, Franklin JM, Avorn J, Landon J, Kesselheim AS. Association of Industry Payments to Physicians With the Prescribing of Brand-name Statins in Massachusetts. *JAMA Intern Med*. 2016;176(6):763-768. doi:10.1001/jamainternmed.2016.1709
71. Hadland SE, Krieger MS, Marshall BDL. Industry Payments to Physicians for Opioid Products, 2013–2015. *Am J Public Health*. 2017;107(9):1493-1495. doi:10.2105/AJPH.2017.303982
72. Hadland SE, Rivera-Aguirre A, Marshall BDL, Cerda M. Association of Pharmaceutical Industry Marketing of Opioid Products With Mortality From Opioid-Related Overdoses. *JAMA Netw Open*. 2019;2(1):e186007. doi:10.1001/jamanetworkopen.2018.6007
73. Powell D, Pacula RL, Taylor E. How Increasing Medical Access to Opioids Contributes to the Opioid Epidemic: Evidence from Medicare Part D. *NBER Work Pap Ser*. 2015;No. 21072. doi:10.3386/w21072
74. Gilson TP, Shannon H, Freiburger J. The Evolution of the Opiate/Opioid Crisis in Cuyahoga County. *Acad Forensic Pathol*. 2017;7(1):41-49. doi:10.23907/2017.005
75. Preliminary 2018 Drug Overdose Death Statistics: Cuyahoga County, Ohio. Office of the Executive. http://executive.cuyahogacounty.us/en-US/2018-Drug-Overdose-Death-Statistics.aspx.
76. Waite K, Decken A, Perch S, Kohler LJ. Carfentanil and Current Opioid Trends in Summit County, Ohio. *Acad Forensic Pathol*. 2017;7(4):632-639. doi:10.23907/2017.053
77. Garrett A. Summit County enters new phase of opioid crisis: Deaths decline, but unknown dangers lurk. *Akron Beacon Journal*. January 20, 2018.
78. Wexelblatt SL, McAllister JM, Nathan AT, Hall ES. Opioid Neonatal Abstinence Syndrome: An Overview. *Clin Pharmacol Ther*. 2018;103(6):979-981. doi:10.1002/cpt.958
79. Hall ES, McAllister JM, Wexelblatt SL. Developmental Disorders and Medical Complications Among Infants with Subclinical Intrauterine Opioid Exposures. *Popul Health Manag*. 2019;22(1):19-24. doi:10.1089/pop.2018.0016
80. Patrick SW, Schumacher RE, Benneyworth BD, Krans EE, McAllister JM, Davis MM. Neonatal Abstinence Syndrome and Associated Health Care Expenditures: United States, 2000-2009Trends in Neonatal Abstinence Syndrome. *JAMA*. 2012;307(18):1934-1940. doi:10.1001/jama.2012.3951
81. Villapiano NLG, Winkelman TNA, Kozhimannil KB, Davis MM, Patrick SW. Rural and Urban Differences in Neonatal Abstinence Syndrome and Maternal Opioid Use, 2004 to 2013. *JAMA Pediatr*. 2017;171(2):194-196. doi:10.1001/jamapediatrics.2016.3750
82. Ko JY, Patrick SW, Tong VT, Patel R, Lind JN, Barfield WD. Incidence of Neonatal Abstinence Syndrome—28 States, 1999–2013. *Morb Mortal Wkly Rep*. 2016;65(31):799-802.
83. Martins SS, Sarvet A, Santaella-Tenorio J, Saha T, Grant BF, Hasin DS. Changes in US Lifetime Heroin Use and Heroin Use Disorder: Prevalence From the 2001-2002 to 2012-2013 National Epidemiologic Survey on Alcohol and Related Conditions. *JAMA Psychiatry*. 2017;74(5):445-455. doi:10.1001/jamapsychiatry.2017.0113
84. Ball JC, Englander DM, Chambers CD. The Incidence and Prevalence of Opiate Addiction in the United States. In: Ball JC, Chambers CD, eds. *The Epidemiology of Opiate Addiction in the United States*. Springfield, IL: Charles C. Thomas; 1970:68-78.
85. Kilmer B, Everingham S, Caulkins J, et al. *What America's Users Spend on Illegal Drugs: 2000-2010*. Santa Monica, CA; 2014.
86. Cicero TJ, Ellis MS, Surratt HL, Kurtz SP. The Changing Face of Heroin Use in the United States: A Retrospective Analysis of the Past 50 Years. *JAMA Psychiatry*. 2014;71(7):821-826. doi:10.1001/jamapsychiatry.2014.366